SUPPORT FOR THE AMENDMENTS

Claim 32 was previously canceled.

Claim 1 has been amended.

Claims 36 and 37 have been added.

The amendment to Claim 1 is supported by the corresponding originally presented claim. Claims 36 and 37 are supported by, at least, page 1, lines 5-30, page 2, lines 1-5, page 4, lines 6-8, and page 9, lines 15-20.

No new matter has been added by the present amendment.

REMARKS

Claims 1-31 and 33-37 are pending in the present application.

The rejection of Claims 1-29, 31, and 33-35 under 35 U.S.C. §103(a) over Alisi et al (US 6,197,769) supplemented with CA129:316219 in view of Catlow et al (US 5,654,320) is respectfully traversed.

The Examiner alleges that Alisi et al disclose a compound that is structurally very close to the compound of Claim 8, wherein the compound of Alisi et al has only two differences from the compound of Claim 8 (CA129:316219 is relied upon for the structure of the compound disclosed by Alisi et al). Specifically, the compound cited by the Examiner differs from the compound of Claim 8 in that the Rb moiety of the compound of Claim 8 is H and Claim 8 contains a proviso requiring that the terminal phenyl to be substituted by other than hydroxyl.

The Examiner alleges that Catlow et al is analogous art wherein it is taught that Rb is optionally unsubstituted or substituted and the terminal phenyl is optionally substituted with non-hydroxyl substituents. Thus, the Examiner concludes that the combination of Alisi et al and Catlow et al would render the present invention obvious.

Applicants respectfully disagree with these allegations and the corresponding assertion that the presently claimed invention would be obvious.

To this end, Applicants submit that the isopropyl substituent of Alisi et al, which corresponds to the Rb moiety of the present invention, is an essential feature of the compounds of Alisi et al (i.e., there is no possibility for substitution and/or modification at this position). As such, the removal or substitution of such an essential feature of Alisi et al would be contrary to the disclosure of Alisi et al and would render the prior art unsatisfactory

for the intended purpose (i.e., antagonism of the 5HT4 receptor by a 1-isopropyl indazole amide compound; MPEP 2143.01(V)).

In addition, at the R6 group of Alisi et al the hydorx substitution of phenyl is another essential feature of Alisi et al as there are no other possible substitutions of the phenyl group. Thus, the introduction of a substitution other than hydroxy would be contrary to the disclosure of Alisi et al and would render the prior art unsatisfactory for the intended purpose (MPEP §2143.01(V)).

With respect to the position corresponding to R6 in the claimed invention, the Examiner alleges that the presently claimed invention contains a "proviso condition requires that the terminal phenyl to be "substituted" by other than hydroxyl". However, the claimed invention does not provide for "any substitution other than hydroxy" on the phenyl ring as argued by the Examiner. The substituents of the phenyl ring are clearly listed and limited to those of Claim 1 (Rc and Rd). Quite simply, these substituents are not disclosed or suggested by Alisi et al and Catlow et al.

Contrary to the Examiner's allegation, Catlow et al is not analogous art. In the previous office action the Examiner clearly stated that Catlow et al compounds differ from the compounds of the present invention for (i) one methylene linker between the indazolyl and the piperidinyl ring, (ii) the rotation of the piperidinyl ring, and (iii) the reverse amidomethyl linkage (this latter being wrong as outlined in the previous response as the actual difference was to substitute an amidomethyllinkage with an ethylene linkage). Furthermore, Applicants submit that Alisi et al and Catlow et al disclose 5HT4 receptor binding compounds for treating gastrointestinal disorders. None of the references disclose or suggest employing the disclosed compounds as analgesic. Further, none of the references

disclose or suggest to modify the disclosed compounds with the reasonable expectation of finding novel analgesic compounds.

Even if Catlow et al can be considered analogous art, there is no disclosure or suggestion for the substitutions listed in the present Claim 1 for Rc and Rd. As a matter of fact, the Examiner only cited four Catlow et al compounds, wherein three of them are unsubstituted and just one has a substitution with a fluorine atom (which is not included in either Rc or Rd.) Moreover, all compounds cited by Catlow et al having a terminal methylenephenyl group are unsubstituted, and only that with the terminal ureidophenyl group is substituted with a fluorine atom.

With the foregoing deficiencies in the Examiner's allegations in mind, Applicants again direct the Examiner to *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) in which the Court of Appeals for the Federal Circuit clearly state that in order to find a *prima facie* case of unpatentability, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required (*Takeda* at 1174, citing *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990); *In re Grabiak*, 769 F.2d 729, 226 USPQ 870 (Fed. Cir. 1985); *In re Lalu*, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984)).

Moreover, as clearly stated by *Takeda* at 1174, the Court squarely addressed the test for *prima facie* obviousness enunciated by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 [82 USPQ2d 1385](2007) in the context of chemical compounds:

> That test for *prima facie* obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.[2] While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation("TSM") test in an obviousness inquiry, the Court

> acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight"to an obviousness inquiry. *Id.* Thus, ***in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.*** (*emphasis added*)

Applicants submit that the present invention is not obvious in view of the combined disclosures of Alisi et al and Catlow et al, as these references fail to provide the requisite reason that would have led a chemist to modify the compounds disclosed therein in the manner necessary to arrive at the claimed compounds. Accordingly, the skilled artisan would not have been motivated by Catlow et al to modify the Alisi et al compounds to arrive at the presently claimed subject matter. On the contrary, as discussed above, the two substitutions that would be required are essential features of Alisi et al and modification of these substituents would render Alisi et al unsatisfactory for the intended purpose (MPEP §2143.01(V)).

Even when combining these disclosures, the result would not have provided the substitutents at Rc and Rd as the combined disclosures would only provide fluorine atoms at Rc and Rd. Thus, the combined disclosures of Alisi et al and Catlow et al fail to support even a *prima facie* case of obviousness.

In view of the foregoing, Applicants request withdrawal of this ground of rejection.

The rejection of Claims 1-29, 31, and 33-35 under 35 U.S.C. §103(a) over Suzuki et al (US 6,096,746) in view of Alisi et al (US 6,197,769) is respectfully traversed.

The Examiner alleges that Suzuki et at generically taught indazolyl piperidine compounds and provided examples (17, 18, and 9) guiding to a compound that only has a methylene difference in the linker between the indazolyl group and the piperidine group with the instant claim.

Further, the Examiner alleges that Alisi et al disclose both the methylene and the ethylene chain linker. Thus, the Examiner concludes that the combination of Alisi et al and Catlow et al would render the present invention obvious.

Applicants respectfully disagree with these allegations and the corresponding assertion that the presently claimed invention would be obvious.

The Examiner is reminded that the isopropyl substituent of Alisi et al, which corresponds to the Rb moiety of the present invention, is an essential feature of the compounds of Alisi et al (i.e., there is no possibility for substitution and/or modification at this position). As such, the removal or substitution of such an essential feature of Alisi et al would be contrary to the disclosure of Alisi et al and would render the prior art unsatisfactory for the intended purpose (i.e., antagonism of the 5HT4 receptor by a 1-isopropyl indazole amide compound; MPEP 2143.01(V)).

In addition, at the R6 group of Alisi et al the hydroxy substitution of phenyl is another essential feature of Alisi et al as there are no other possible substitutions of the phenyl group. Thus, the introduction of a substitution other than hydroxy would be contrary to the disclosure of Alisi et al and would render the prior art unsatisfactory for the intended purpose (MPEP §2143.01(V)).

With respect to Suzuki et al, this reference does not provide for any substitution of the phenyl ring other than the fluorine atom. Accordingly, there is no disclosure or suggestion for the substitutions listed in the present Claim 1 for Rc and Rd.

With the foregoing deficiencies in the Examiner's allegations in mind, Applicants again direct the Examiner to *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) in which the Court of Appeals for the Federal Circuit clearly state that in order to find a *prima facie* case of unpatentability, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required (*Takeda* at 1174, citing *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990); *In re Grabiak*, 769 F.2d 729, 226 USPQ 870 (Fed. Cir. 1985); *In re Lalu*, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984)).

Moreover, as clearly stated by *Takeda* at 1174, the Court squarely addressed the test for *prima facie* obviousness enunciated by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 [82 USPQ2d 1385](2007) in the context of chemical compounds:

> That test for *prima facie* obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.[2] While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight"to an obviousness inquiry. *Id.* Thus, ***in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.*** (*emphasis added*)

Applicants submit that the present invention is not obvious in view of the combined disclosures of Alisi et al and Suzuki et al, as these references fail to provide the requisite

reason that would have led a chemist to modify the compounds disclosed therein in the manner necessary to arrive at the claimed compounds. Accordingly, the skilled artisan would not have been motivated by Alisi et al to modify the Suzuki et al compounds to arrive at the presently claimed subject matter. Even when combining these disclosures, the result would not have provided the substitutents at Rc and Rd as the combined disclosures would only provide flurine atoms at Rc and Rd. Thus, the combined disclosures of Alisi et al and Suzuki et al fail to support even a *prima facie* case of obviousness.

In view of the foregoing, Applicants request withdrawal of this ground of rejection.

The rejection of Claims 1-29, 31, and 33-35 under 35 U.S.C. §103(a) over Schaus et al (J. Med. Chem. 1998) in view of Patani is respectfully traversed.

The Examiner alleges that Schaus et at disclose compound 19d (page 1948, table 3) as being a compound that is "close" structurally to the claimed compounds. Further, the Examiner alleges that Patani discloses that amide bond and reverse amide bond are bioisosters. Thus, the Examiner concludes that the combination of Schaus et al and Patani would render the present invention obvious.

Applicants respectfully disagree with these allegations and the corresponding assertion that the presently claimed invention would be obvious.

Applicants direct the Examiner's attention to page 3171 of Patani (Table 49, compounds 98a and 98b). Based on this disclosure, Patani clearly discloses that replacement of reverse amide bond (NHCO) with amide bond (CONH) provided a reduction of activity. Other structures are mentioned to replace the NHCO group and retaining activity (compounds 98d-e-g-f). Accordingly, contrary to the Examiner's allegations, the skilled artisan would not

be motivated by Patani to modify the Shaus et al compound to arrive at the presently claimed invention as Patani discloses that such a modification would lead to a decrease in activity.

The Examiner is reminded that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Thus, this disclosure by Patani actually defeats the prima facie obviousness case, not supports it.

Moreover, the precedent of *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) remains relevant to this rejection where the Court of Appeals for the Federal Circuit clearly state that in order to find a *prima facie* case of unpatentability, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required (*Takeda* at 1174, citing *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990); *In re Grabiak*, 769 F.2d 729, 226 USPQ 870 (Fed. Cir. 1985); *In re Lalu*, 747 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984)).

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> That test for *prima facie* obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.[2] While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S. Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a

> "rigid and mandatory" formula, that test can provide "helpful insight"to an obviousness inquiry. *Id.* Thus, ***in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.*** (*emphasis added*)

Applicants submit that the present invention is not obvious in view of the combined disclosures of Shaus et al and Patani, as these references fail to provide the requisite reason that would have led a chemist to modify the compounds disclosed therein in the manner necessary to arrive at the claimed compounds. Thus, the combined disclosures of Shaus et al and Patani fail to support even a *prima facie* case of obviousness.

In view of the foregoing, Applicants request withdrawal of this ground of rejection.

The obviousness-type double patenting rejection of Claims 1-29, 31, and 33-35 over Alisi et al (US 6,197,769) in view of Patani is respectfully traversed.

The Examiner alleges that Alisi et al disclosed compounds wherein the phenyl moiety is unsubstituted or optionally hydroxyl substituted. The Examiner alleges that Patani suggests to replace the CONHCH2 linker of Alisi et al compounds with other amide bond linkers (NHCO or NHCOCH2). Thus, the Examiner concludes that the combination of the claims of Alisi et al and Patani would render the present invention obvious.

Applicants respectfully disagree with these allegations and the corresponding assertion that the presently claimed invention would be obvious. Alisi et al and Patani are discussed above.

First, Alisi et al only claim compounds having hydroxy substituted phenyl. Alisi et al did not disclose unsubstituted or optionally hydroxy-substituted phenyl. The substitution of the phenyl with hydroxy is an essential feature of Alisi et al. Then the removal of the

hydroxy or the introduction of a substitution other than hydroxy would be contrary to the disclosure of Alisi at al and would render the prior art unsatisfactory for the intended purpose (MPEP §2143.01(V)).

Further, Applicants direct the Examiner's attention to page 3171 of Patani (Table 49, compounds 98a and 98b). Based on this disclosure, Patani clearly discloses that replacement of reverse amide bond (NHCO) with amide bond (CONH) provided a reduction of activity. Other structures are mentioned to replace the NHCO group and retaining activity (compounds 98d-e-g-f). Accordingly, contrary to the Examiner's allegations, the skilled artisan would not be motivated by Patani to modify the Shaus et al compound to arrive at the presently claimed invention as Patani discloses that such a modification would lead to a decrease in activity.

The Examiner is reminded that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Thus, this disclosure by Patani actually defeats the prima facie obviousness case, not supports it.

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Applicants submit that the present invention is not obvious in view of the combined disclosures of the claims of Alisi et al and Patani, as these references fail to provide the requisite reason that would have led a chemist to modify the compounds disclosed therein in the manner necessary to arrive at the claimed compounds. Thus, the combined disclosures of the claims of Alisi et al and Patani fail to support even a *prima facie* case of obviousness.

In view of the foregoing, Applicants request withdrawal of this ground of rejection.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
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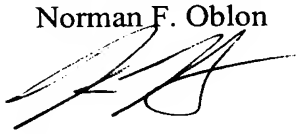
Norman F. Oblon



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